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Society for Immunotherapy of Cancer (SITC) recommendations on intratumoral immunotherapy clinical trials (IICT): from premalignant to metastatic disease

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ABSTRACT

Background Intratumorally delivered immunotherapies have the potential to favorably alter the local tumor microenvironment and may stimulate systemic host immunity, offering an alternative or adjunct to other local and systemic treatments. Despite their potential, these therapies have had limited success in late-phase trials for advanced cancer resulting in few formal approvals. The Society for Immunotherapy of Cancer (SITC) convened a panel of experts to determine how to design clinical trials with the greatest chance of demonstrating the benefits of intratumoral immunotherapy for patients with cancers across all stages of pathogenesis.

Methods An Intratumoral Immunotherapy Clinical Trials Expert Panel composed of international key stakeholders from academia and industry was assembled. A multiple choice/free response survey was distributed to the panel, and the results of this survey were discussed during a half-day consensus meeting. Key discussion points are summarized in the following manuscript.

Results The panel determined unique clinical trial designs tailored to different stages of cancer development—from premalignant to unresectable/metastatic—that can maximize the chance of capturing the effect of intratumoral immunotherapies. Design elements discussed included study type, patient stratification and exclusion criteria, indications of randomization, study arm determination, endpoints, biological sample collection, and response assessment with biomarkers and imaging. Populations to prioritize for the study of intratumoral immunotherapy, including stage, type of cancer and line of treatment, were also discussed along with common barriers to the development of these local treatments.

Conclusions The SITC Intratumoral Immunotherapy Clinical Trials Expert Panel has identified key considerations for the design and implementation of studies that have the greatest potential to capture the effect of intratumorally delivered immunotherapies. With more effective and standardized trial designs, the potential of intratumoral immunotherapy can be realized and lead to regulatory approvals that will extend the benefit of these local treatments to the patients who need them the most.

INTRODUCTION

While systemic immunotherapies are now closely integrated into treatment regimens across stages of malignancies, the development of intratumoral immunotherapies has been more complicated. In early-stage cancers, multiple locally delivered agents have progressed to full US Food and Drug Administration (FDA) approval (table 1). In the metastatic setting, however, only one intratumoral agent has been approved with mixed results from late-phase combination clinical trials.[1–4] To increase the likelihood of success for intratumoral immunotherapy development, the Society for Immunotherapy of Cancer (SITC) convened an Expert Panel Consensus Meeting. The panel agreed that intratumoral immunotherapy has the potential to help patients achieve locoregional control and in some cases prevent locoregional recurrence and distant metastases, highlighting its potential efficacy in all stages of cancer, from premalignant to metastatic disease.[1 5–10] Defining the subset of patients for whom intratumoral

Table 1 FDA-approved locally delivered immunotherapies[76]

Locally administered or delivered immunotherapy and FDA approval date	FDA indication and route of administration	Category of agent	Study endpoint(s) supporting approval
Efudex (Fluorouracil)*[77] 1970	"… treatment of multiple actinic or solar keratoses. In the 5% strength, it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites." *Topical solution, 2% or 5%*	5-fluoro-2,4 (1H,3H)-pyrimidinedione	At 1 year after treatment, 39 of 198 patients treated with fluorouracil cream (two times per day for 4 weeks) had tumor residue or recurrence; 80.1% (95% CI 74.7% to 85.9%) of these patients were tumor-free at 3-month and 12-month follow-up.[78–80]
BCG 1990	Treatment and prophylaxis of CIS of the bladder urothelium, and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following TUR. Not recommended for stage TaG1 papillary tumors, unless they are judged to be at high risk of tumor recurrence.† *Intravesical instillation*	Attenuated strain of *Mycobacterium bovis*	Recurrence rate for patients with a history of recurrent superficial TCC of the bladder: 0% (BCG group) vs 40% (thio-tepa group)[81] For Patients with Ta/T1 tumors without CIS: ► Estimated probability of being disease free at 5 years: 37% (BCG group) vs 17% (doxorubicin group; p=0.015) ► Median time to treatment failure‡: 22.5 (BCG group) months vs 10.4 months (doxorubicin group)[82] For patients with CIS: ► Complete-response probability estimates§: 70% (BCG group) vs 34% (doxorubicin group; p<0.001) ► Median time to treatment failure‡: 39 months (BCG group) vs 5.1 months (doxorubicin group)[82]
Imiquimod 2004	Biopsy-confirmed, primary superficial basal cell carcinoma in adults with normal immune systems.¶ *5% cream, topical application*	TLR-7/8 agonist	Histological clearance rates: ► Imiquimod treatment groups: 82% (5 times per week) and 79% (7 times per week) ► Vehicle group: 3%[8]
T-VEC October 27, 2015	Treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. *Intratumoral injections into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound*	Genetically modified attenuated HSV-1 oncolytic virus	DRR**: 16.3% (intralesional T-VEC) vs 2.1% (subcutaneous GM-CSF)[1]
Nadofaragene firadenovec-vncg December 16, 2022	High-risk BCG unresponsive NMIBC with CIS with or without papillary tumors.†† *Intravesical instillation*	Non-replicating adenoviral vector-based gene therapy	CR‡‡: 51% (95% CI 41% to 61%) DOR: 9.7 months (range 3 to 52+)[83]

*Although 5-FU is a chemotherapy, not an immunotherapy per se, it can act as an immune modulator[84 85] and intratumoral chemotherapy efficacy relies on the immune system.[86–88]
†Per AUA/SUO and SITC, induction and 1 year or 3 years of maintenance therapy should be considered for intermediate-risk disease and high-risk disease, respectively.[89 90]
‡Time to treatment failure was defined as termination of treatment due to persistence, recurrence, or progression of disease.
§Complete-response probability estimates were defined as the estimated probability of documented disappearance of disease.
¶Imiquimod is also FDA approved for other non-cancerous skin conditions,[91] with off-label uses for melanoma in situ (lentigo maligna type), early-stage mycosis fungoides, and penile cancer (Tis or Ta disease).[92]
**DRR was defined as an objective response lasting continuously ≥6 months.
††CR was defined as negative cystoscopy with applicable TURBT and biopsies and urine cytology.
‡‡Approval based on a single-arm study.
AUA, American Urological Association; BCG, Bacillus Calmette–Guérin; CI, confidence interval; CIS, carcinoma in situ; CR, complete response rate; DOR, median duration of response; DRR, durable response rate; FDA, Food and Drug Administration; FU, fluorouracil; 5-FU, 5-fluorouracil; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HSV-1, herpes simplex virus-1; NMIBC, non-muscle invasive bladder cancer; SITC, Society for Immunotherapy of Cancer; SUO, Society of Urologic Oncology; TCC, transitional cell carcinoma; TLR, toll-like receptor; TUR, transurethral resection; TURBT, transurethral resection of bladder tumor; T-VEC, talimogene laherparepvec.

immunotherapy may prevent locoregional or distant metastatic disease remains critically important.

Increased awareness of intratumoral immunotherapy was identified as a priority during the 2021 SITC Strategic Retreat to facilitate trial enrollment for agents in development and increase high-yield referrals for approved agents. There is currently a lack of consensus for standardized trial design for intratumoral immunotherapy, resulting in wasted resources and potentially the loss of invaluable disease-free patient years. SITC convened an international panel of experts in the field of intratumoral immunotherapy to develop recommendations that will help studies optimally capture the potential unique benefit of intratumoral agents used in the (secondary) preventive, neoadjuvant, and unresectable/metastatic settings. These recommendations address an unmet need for standardized, generalizable trials designed with the logistical challenges, pharmacokinetics, mechanisms of action, and limited systemic toxicities of intratumoral immunotherapy in mind. Other topics addressed include how to navigate intratumoral-specific regulatory approval standards, integration of intratumoral therapies into standard of care (SOC) practice, and the optimal use of biomarkers.

Immunotherapy, for the purposes of this manuscript, refers to any treatment administered with the intent of eliciting a host anticancer immune response and could, therefore, be extended to targeted radiotherapy, thermal or electrical pulse ablation, intratumoral chemotherapy, intratumoral immune checkpoint blockade (ICB), recombinant cytokines[11 12] and immune adjuvants, etc. The term intratumoral was preferred by this panel as it was deemed more specific than alternative terms such as intralesional, and for the purposes of this manuscript refers to any treatment directed at a specific tissue with the intent of eliciting a host anticancer immune response. Therefore, the trial design recommendations herein apply to any intratumoral treatment directed at a primary or metastatic lesion, but could also be extended to postresection scars, peritumoral area, draining lymph nodes (LNs),[13] etc. Likewise, "injected" lesions could be extended to tissue that has received drug via direct injection, peritumoral injection, topical application, embolization, or targeted irradiation insofar as it aims to trigger a host antitumor immune response. And finally, in order to maintain a relevant scope, only a small number of specific intratumoral immunotherapies are mentioned throughout this manuscript for illustrative purposes.

METHODS

A SITC leadership group determined the composition of the SITC Intratumoral Immunotherapy Clinical Trials (IICT) Expert Panel with the goal of including international stakeholders from academia, industry, and regulatory agencies. Conflict of interest disclosures were provided by each of the panel members and are published along with this manuscript. A multiple choice/free response survey on key elements for panel discussion was developed by the IICT leadership group and distributed to the IICT panel. A half-day consensus meeting was then held where panel members heard state of the field presentations and discussed survey results in order to come to agreement on the recommendations summarized in this manuscript. The funding for the convening of the consensus meeting and development of this manuscript was provided solely by SITC.

RATIONALE FOR INTRATUMORAL APPROACHES

Intratumoral delivery of immunotherapy offers potentially important advantages to patients, including the potential to increase local drug concentration without additional systemic exposure and toxicity[14] and elicit antitumor immune responses[15] that potentially induce systemic responses with regression of non-injected lesions,[16–18] establishing tumor-specific immunosurveillance to prevent future recurrence of disease. To investigate the full antineoplastic potential of immunotherapy, intratumoral delivery should be prioritized for study with trials tailored to the molecular and cellular characteristics of the tumor microenvironment (TME) in both injected and non-injected lesions, which are critical for the underlying mechanisms of action for most intratumoral immunotherapy agents. The TME changes as it moves through the three phases of immunoediting—immunosurveillance, equilibrium, and finally escape resulting in metastatic tumor growth.[19] Furthermore, tumor immune evasion occurring during epithelial-to-mesenchymal transition (EMT) is associated with increased immunosuppressive cells and immune checkpoint expression, and this immunosuppression in turn induces further EMT in tumor cells.[20] Together with EMT, chromosomal instability turns cancer cells resistant to host immune attack[21] and anticancer therapies both in vivo and in vitro.[22–24] Intratumoral immunotherapy can create a more favorable TME in the injected tumor by recruiting/expanding and activating antitumor effector T-cells[25] and B-cells,[26] depleting regulatory T-cells,[27] re-educating macrophages to destroy tumor stroma,[28] IFN-γ gene expression,[29] and recruiting dendritic cells[30] among other mechanisms. Another advantage of intratumoral or peritumoral delivery of immunomodulatory agents is optimal access to tumor-draining LNs (TDLN). TDLNs are often immune suppressed and thereby hampered in their vital function of eliciting local and systemic immune protection against metastatic spread.[31 32] There is accumulating evidence that it is vital to address TDLNs in order to secure immunotherapy efficacy[33 34] and that their local conditioning can secure systemic antitumor immunity.[35–37]

Intratumoral delivery of immunotherapy is practical and mechanistically rational to achieve local control and may elicit locoregional or even systemic immune responses to benefit patients. It can be administered

via direct visualization, implantation of a delivery port, endoscopically, bronchoscopically, or with image-guidance.[38] Intratumoral immunotherapy can be used for a variety of different malignancies and with many agents, including but not limited to mRNAs, oncolytic viruses, toll-like receptor (TLR) and other pattern recognition receptor agonists, CD40 agonists, cytokines (eg, IL-12, IL-2, IFN-alpha[11 12]), intratumoral ICB, or intratumoral cytotoxics (including chemotherapies).[14] Intratumoral delivery of drug limits the risk for systemic toxicity allowing for higher intratumoral drug concentration (eg, in tumors localized to the central nervous system (CNS) where penetrance of systemically administered drugs may be low) and may expand access to immunotherapy, for example, for patients with comorbidities (eg, history of autoimmunity), poor Eastern Cooperative Oncology Group performance status (ECOG PS), solid organ transplant recipients, and for patients with earlier stages of disease for whom perioperative systemic therapy side effects are less acceptable. Intratumoral immunotherapy also offers an alternative localized approach to potentially morbid surgeries. Recent phase 2 and 3 trials of intratumoral immunotherapy for advanced melanoma that failed to meet their endpoints[2–4] have unfortunately cultivated a bias against the development of these drugs, and careful clinical trial design to select the appropriate population who will benefit from intratumoral immunotherapy is required.

RECOMMENDATIONS FOR INTRATUMORAL IMMUNOTHERAPY TRIAL DESIGN

Common considerations

When considering the current state of intratumoral immunotherapy for advanced cancer, the lack of phase 2/3 trial success, notwithstanding well documented activity in smaller proof of concept studies, is an obvious starting point. Patient-specific factors, disease characteristics (including predictive biomarkers), agent selection and sequencing, measurement and evaluation of trial endpoints, and delivery approaches (including experience in their clinical application) all may have contributed to the inability of recent trials to meet their survival and response endpoints: MASTERKEY-265 (intratumoral oncolytic virus; phase 3), ILLUMINATE-301 (intratumoral TLR agonist; phase 3), and KEYNOTE-695 (in situ mRNA electroporation; phase 2). Indeed, some traditional methods such as response evaluation criteria in solid tumors (RECIST) v1.1 objective response rate (ORR) and progression-free survival (PFS) might not be adapted to demonstrate efficacy of intratumoral immunotherapies. Randomization of phase 2 trials and better patient stratification of phase 3 randomized trials may improve the ability of a study to capture the clinical benefit of intratumoral immunotherapy. Stratification factors to consider include lactate dehydrogenase (LDH)>upper limit of normal (ULN), liver metastasis, and cancer-specific factors such as human papilloma virus (HPV) status in head and neck squamous cell carcinoma and cervical cancer. More clinically relevant endpoints integrating overall responses and their durability (eg, durable clinical benefit (DCB), which is the fraction of patients maintaining an objective response or a stable disease at a prespecified time point based on the disease, such as 6 months), and biomarker-based patient selection are other strategies to improve the ability of trials to capture intratumoral immunotherapy effect. Additionally, the optimal sequencing of injected lesions with systemic therapy is an important question that remains to be answered in the field. Heterogeneity between operators/sites/countries and a lack of protocol adherence (eg, not completing the originally proposed number of injections), transition from experienced to inexperienced sites, and inconsistent injection technique (leading to variability in the degree of extravasation, injection into necrotic tissue, injection into a tumor, ie, the wrong size, amount of pressure with delivery, number of tumor punctures, etc) could impact clinical results as well. Better site training for standardized practice and consistent technique is critical to capture the efficacy of intratumoral agents. Indeed, in the subset analysis of the MASTERKEY-265 PFS results, intratumoral oncolytic virus plus anti-PD-1 performed better than anti-PD-1 alone for patients having low LDH, smaller tumor lesions, or when injected into patients in the US.[39] Therefore, negative advanced phase trials are a valuable learning opportunity not to be disregarded or used as a reason to deprioritize further development of intratumoral agents. This panel kept these as well as other ongoing trials in mind when discussing aspects of intratumoral immunotherapy trial design applicable across all disease stages, which are summarized in box 1.

Site selection

The IICT Expert Panel agreed that a solid infrastructure and close working relationships between clinicians from different specialties were essential for sites where intratumoral immunotherapy studies are to be conducted. Those in favor of conducting trials only at academic hospitals pointed out the importance of integrated site expertise (eg, close working habits in the constraints of clinical trials between oncologists, interventional radiologists, radiologists, and surgical oncologists), having a pre-existing immune-monitoring infrastructure, the need for provider experience in delivering all types (including prior lines) of immunotherapy, and the necessary availability of specialists outside of medical oncology to be “modality-specific champions” of the delivery technique or the management of organ specific adverse events (AEs) (eg, dermatologists, interventional radiologists, surgeons, pulmonologists, etc). Some panel members further asserted that more complex or earlier phase trials

Box 1 Direction for intratumoral immunotherapy trial design common to all disease states

- ⇒ Site selection: initially at comprehensive cancer centers with potential expansion to community sites to improve generalizability.
- ⇒ Exclusion criteria: disease-specific or patient-specific factors that would preclude intratumoral injection or (measurement of) response due to safety, mechanistic, or logistical barriers.
- ⇒ Stratification factors: use previous studies to determine which factors will have the greatest impact on efficacy (eg, liver metastasis, LDH, etc).
- ⇒ Safe and effective dose to take into definitive trials: determine using an intratumoral monotherapy cohort followed by an intratumoral therapy plus systemic therapy combination cohort; could consider using an intratumoral monotherapy cohort with simultaneous/parallel enrollment into an intratumoral therapy plus systemic therapy combination cohort if overlapping toxicities are expected to be limited. In accordance with FDA Project Optimus guidelines, there is a need to identify alternative dosing justification based on the underlying mechanism(s) of action (ie, dose escalation should be appropriately done to allow for significant number of patients per dose level to ensure optimal modified dose is reached, especially when the MTD is not expected to be your optimal biological dose).[42 43]
- ⇒ Phase 2 endpoints for:
  - ⇒ Neoadjuvant treatment (randomized trials): RECIST or iRECIST presurgery, pCR at surgery (note: pCR for intratumoral immunotherapy is not comparable to pCR for systemic immunotherapy in terms of predicting RFS[7]), ctDNA levels postsurgery, time to next therapy (including surgery, radiation therapy, systemic drug, etc), down staging (turning inoperable tumors into operable), RFS, OS; survival endpoints for non-translational studies are strongly preferred.
  - ⇒ Neoadjuvant treatment (single-arm trials): EFS/RFS and their correlation to pCR (complete absence of viable tumor in the treated tumor bed) or near-pCR/major pathological response versus pathological non-response.[93]
  - ⇒ Unresectable/metastatic treatment: DCB or landmark PFS may be preferred over ORR and/or median DOR, OS.
- ⇒ Randomization of phase 2 trials: preferred in most instances, including appropriate control arms.
- ⇒ Serial tissue collection: recommended in early phase for target and pharmacodynamics assessment in order to demonstrate target expression, saturation and engagement.
- ⇒ Response assessment: should include measurement and number of injected and non-injected lesions as well as potentially the ratio of injected to non-injected lesions, target and non-target lesions via RECIST v1.1 allowing for treatment and response beyond progression to be captured. Response per itRECIST, irRECIST, or iRECIST may be exploratory to correlate with RECIST v1.1 data. Target lesions must include non-injected lesions.
- ⇒ Biomarkers: comprehensive ancillary biomarker programs should be coupled to early-stage intratumoral drug development. Cancer patients are currently being treated in a blinded fashion although all new treatments are specific to a therapeutic target; a better analysis of the expression and engagement of therapeutic targets would make it possible in the near future to better select patients who could actually benefit from these new treatments.

should initially enroll only at comprehensive cancer centers. Those in favor of conducting trials at any center with the interest in and capability of performing intratumoral immunotherapy trials (ie, including community hospitals) argued that if site selection is too restrictive, then resulting data may not be generalizable, particularly if an intratumoral agent is targeted for eventual use in the community. Regardless of site, the group agreed that interventionalists (eg, interventional radiologists, pulmonologists, gastroenterologists) should be named co-investigators as they need to be invested in good injection technique and could complete a credentialing program and use a template structure for documenting each injection.

Exclusion criteria

With regard to exclusion criteria, the panel identified several factors that would necessarily preclude intratumoral immunotherapy trial participation, including difficult to access lesions, painful or large necrotic lesions, the presence of non-injectable lesions (depending on trial endpoints), proximity to large vessels or critical structures, extensive visceral disease, symptomatic CNS disease, extensive tumor burden, and lesions (injected and non-injected) that cannot be measured. Patient-specific exclusion criteria included coagulopathy, bleeding disorders, life-threatening autoimmune disease, poor ECOG PS, and multiple comorbidities. Further, special attention should be paid to the use of specific intratumoral immunotherapy agents in patients with compromised immune systems (eg, solid organ transplant patients, chronic immunosuppression).

Stratification factors

The panel agreed that stratification should account for the disease setting and experimental agent and should be modeled after previous studies to predict which factors will have the greatest impact on efficacy. In addition to patient-specific factors such as age and ECOG PS, the group identified the following factors that could be used for stratification: the presence of visceral (particularly liver) metastases, tumor markers (eg, LDH above normal[40], etc), tumor immunogenicity (potentially defined by tumor mutational burden (TMB)), stage, size or number of lesions, disease burden (eg, prostate-specific antigen (PSA) elevated in prostate cancer), distant metastases, previous response to (ICB) therapy, HPV status for certain cancers, tumor type, or PD-L1 status.

Safe and effective dose to take into definitive trials

The optimal biological dose of intratumoral therapies may sometimes be informed by pharmacodynamic readouts of preclinical assays (as demonstrated in Maurer *et al*,[41] and dose escalation should be done with a significant number of patients per dose level to ensure that the optimal therapeutic dose is reached[42 43]), which is particularly important when the maximum tolerated dose (MTD) is not expected to be the same as the optimal biological dose. The majority of the expert panel agreed that the safe and effective dose of an intratumoral agent to take into definitive trials should be based on data

from an intratumoral monotherapy cohort followed by an intratumoral therapy plus systemic therapy combination cohort, pointing out the need to clearly demonstrate single-agent activity independent of synergism with a systemic agent, particularly for non-injected lesions. The remainder of the group elected for determination of this dose to be based on an intratumoral monotherapy cohort with simultaneous/parallel enrollment into an intratumoral therapy plus systemic therapy combination cohort, arguing that in most cases, overlapping intratumoral and systemic agent toxicities are expected to be limited. If the development goal is to combine the intratumoral agent with a systemic agent, however, then the intratumoral monotherapy portion of the study could be limited. Depending on strength of preclinical characterization, it may be advisable to robustly investigate multiple doses and/or schedules prior to moving to definitive trials in order to satisfy regulatory considerations.

Trial design

While there are multiple options for the design of phase 1 trials, some of which were discussed by the expert panel, no consensus was reached among the group on optimal phase 1 intratumoral trial design. The group agreed that a typical 3+3 design is not well adapted for studying intratumoral immunotherapy as more patients per dose level, more data points, and a different assessment of pharmacodynamic impact and level of immune activation associated with the drug are needed. Trials of intratumoral therapy require more of a composite analysis including early efficacy, safety, pharmacodynamics, and markers of immune activation from blood and tissue analyses of injected and most importantly non-injected lesions. There was consensus that adequate safety and biology be explored at each dose level and that the optimal study design might vary. This is particularly important in intratumoral therapies where the MTD may not be the most biologically active dose.

Measuring response in phase 2 neoadjuvant and unresectable/metastatic trials

The majority of the panel thought that phase 2 trials in the neoadjuvant and unresectable/metastatic settings should include a measure of response as a primary endpoint preferably in both injected and non-injected tumors to ascertain systemic efficacy (see the discussions on **Sample collection** and **Efficacy assessment**, below). In this setting, local pathological responses need to be scored and their association to recurrence-free survival (RFS) established; currently, perioperative or neoadjuvant immunotherapy effect on pathological complete response (pCR) is incommensurate with RFS. This was exemplified in the primary analysis[7] of neoadjuvant talimogene laherparepvec (T-VEC), where many patients who did not achieve pCR at surgery remained recurrence free at the time of analysis and, as the authors noted, the presence of apparent visible residual tumor at surgery did not associate with a poor response. Indeed, durable improvements in RFS and overall survival (OS) were also demonstrated at the 5-year follow-up of neoadjuvant T-VEC,[44] despite a low rate pCR at the early analysis. Therefore, as some analyses of resected tumors are not predictive of OS, caution should be used in interpretation of these readouts. Also, event-free survival (EFS) is an important measure to capture those who progress prior to surgery, as well as events defined in the RFS. With regard to trials conducted in the unresectable/metastatic setting, response rates can be misleading and DCB or landmark PFS are preferred when high ORRs have not translated into phase 3 trial success, and where phase 3 trial successes have been realized with low response rates.[45 46] With regard to measuring response on imaging, in addition to traditional endpoints based on RECIST v1.1, investigators may collect data that would allow exploratory analysis using novel immunotherapy criteria such as iRECIST and itRECIST. This means allowing therapy past RECIST v1.1 progression in clinically stable subjects, measuring new lesions when possible, and carefully documenting which lesions are injected at each treatment visit, especially those chosen for quantitative assessment (ie, “target” lesions in RECIST terms).

Randomization of phase 2

The panel agreed that randomization of phase 2 trials, possibly with two dose levels, is generally preferred as randomized data are more likely to support FDA approvals. If randomized phase 2 data do not lead directly to approval, then the potential for expansion into a phase 3 trial could still expedite drug development. Furthermore, single-arm data for any agent can be misleading, and comparison to SOC is preferred when the intratumoral drug is planned for use in combination with a systemic agent. Randomization should be used as an opportunity to introduce surrogate biomarkers of efficacy as well. The group also agreed that the decision to randomize phase 2 trials depends on the nature, intent, design, and goal of the trial as well as existing indications and unmet need for the specific cancer under study. For example, for patients whose cancer has progressed through multiple lines of therapy, particularly prior immunotherapy, an SOC comparison may not exist. Also, for biomarker based (tumor agnostic) patient selection, a standard or ethical comparison may not be established. Furthermore, there can be value in determining efficacy of an intratumoral drug regimen in a phase 2 study prior to randomization, particularly when a homogeneous population is needed to demonstrate effect and leverage a phase 3 trial. The group agreed that a Simon 2 stage design[47] with clear futility rules is optimal for phase 2 trials of intratumoral agents.

Sample collection

The expert panel agreed that mandatory serial tissue collection of injected lesions is recommended in early-phase intratumoral immunotherapy clinical trials for target and pharmacodynamics assessments unless it is

unsafe (eg, a difficult trajectory or proximity to large vessels) or not feasible (eg, when tissue collection would compromise the ability to inject or assess a lesion). Tumor biopsies of an uninjected lesion can also be performed for documentation of systemic antitumor effects (abscopal (tumor response in uninjected lesions without concomitant systemic therapy) or anenestic (tumor response in uninjected lesions in the context of concomitant systemic therapy such as intravenous anti-PD-1 such that the effect might be related to the systemic therapy rather than a consequence of the intratumoral therapy)), although priority should be given to analysis of the injected lesion. Furthermore, any tissue collection, but particularly collection of non-injected lesions, should involve thorough patient education to facilitate informed consent. While serial tissue collection is generally not feasible for larger phase 3 trials, it is compatible with phase 1 and 2 studies. For example, serial tissue collection can be used during dose escalation to inform further dosing (eg, to monitor for a bell shape curve effect), in a randomized phase 2 substudy, or during a phase 1 study at a dose selected for further evaluation to determine which biomarkers are most relevant to carry through to larger studies. Regardless of when it is introduced, the group agreed that serial tissue sampling of non-injected lesions (when present) would help to establish a systemic and potentially durable response that could reinforce the value of the treatment for a registration trial. Additional tissue collection factors to consider include the use of fresh tissue biopsy (supernatant) analysis, which is still experimental but may provide valuable information, and evaluation of TDLN tissue. Peripheral blood should be also collected to measure systemic immune responses with markers including plasma (eg, for cytokines and soluble factor titration), serum (eg, for antibody titration), peripheral blood mononuclear cells (PBMCs), circulating tumor DNA (ctDNA), and coding DNA (cdDNA).

Efficacy assessment

The duration and magnitude of response overall and of injected versus non-injected lesions separately should be assessed, taking into account how representative the target lesions are for the total burden of potentially injectable lesions. While there are several exploratory endpoint response criteria that can be useful for monitoring and recording responses of lesions to intratumoral immunotherapy during trial investigation, such as itRECIST,[48] irRECIST,[49] and iRECIST,[50] some of the panelists recognized that these tools can be very cumbersome for investigators. Using standard RECIST v1.1[51] allowing for treatment and response collection beyond progression could be used as the primary method for response assessment recording injected and non-injected lesions and measuring new lesions when possible. However, the protocol should detail how the data beyond progression should be reported in the case report form, notably when uninjected lesions become injected and especially if these lesions were initially part of the RECIST target lesions.

The authors also acknowledge the benefit of highly active injected local immunotherapies that may have limited impact on OS or systemic efficacy but still have value in some clinical situations. For example, local intratumoral treatment of cutaneous metastases (which are often difficult to manage) in patients with triple-negative breast cancer could significantly improve the quality of life of patients. Thus, repeated local administration should be permitted when there is benefit to factors such as quality of life. This is a limitation with current traditional response criteria and may require revisiting appropriate endpoints and assessments to capture all types of benefit.

Biomarkers

While the expert panel was unable to identify a core set of universal biomarkers of response to intratumoral immunotherapy, there was agreement that biomarkers should match the mechanism of action of the drug. Several important tissue-based biomarkers (which may depend on the agent under study) were identified, including markers of T-cell clonality, TME immunophenotype, tumor-infiltrating lymphocytes (TILs), regulatory T-cells (Tregs), dendritic and T-cell activation markers, markers of exhaustion/suppression, IFNγ gene expression signature, and spatial profiling (RNA, protein). Important blood-based biomarkers of response were also identified, including PBMCs, clonality of T-cell response, ctDNA, cdDNA, immunophenotyping, circulating cytokines/chemokines, gene expression signatures, neoantigen expression, and viral titers and antidrug antibodies for oncolytic viruses. Molecular imaging might aid the identification of local versus abscopal effect from locally delivered immunotherapies.[52] However, further research is needed to qualify optimal radiotracers to be used for immune monitoring of these patients.

Preventive intralesional immunotherapy for premalignant lesions

Intralesional immunotherapy may be especially useful for treatment of early premalignant lesions. Conceptually, the rationale for premalignant lesions also applies to early-stage (T1) lesions, for which the safety profile of systemic therapy may not be acceptable. In many cases, these represent fewer lesions for injection, may be smaller in volume requiring less drug exposure, and allow for treatment during the immune surveillance period. Furthermore, the generally tolerable safety profile of intralesional agents may be especially appropriate for premalignant lesions and could provide an alternative to disfiguring or invasive procedures. The panel specifically considered the role of intralesional immunotherapy for studies in patients with premalignant lesions and made recommendations for studies in this patient population.

For the purposes of this manuscript, “premalignant” is defined as any tissue that has the potential to become

Box 2 Preventive intralesional immunotherapy for premalignant lesions

- ⇒ Study population: patients with lesions at a higher risk of progression that are not amenable to surgery, or for which surgery would incur a high level of morbidity.
- ⇒ Endpoints for non-randomized trials: pretreatment and post-treatment pathological features (eg, dysplasia, immune infiltrate) of injected and non-injected lesions; time to relapse, malignancy, or new lesions.
- ⇒ Endpoints for randomized trials: EFS, with a composite of morbid events such as malignant transformation, progression or recurrence of lesion, or need for radiation, ablation, or surgery.
- ⇒ Tissue collection timing: 48 hours to 1 week following first dose for most agents, that is, prior to the onset of necrosis but after TILs can be demonstrated; serial collection thereafter if feasible for up to 1 year.
- ⇒ Note: There was no consensus among the expert panel regarding the value of studying intratumoral immunotherapy for premalignant lesions.

malignant without being histologically classified as malignant. This definition includes, for example, adenomatous colon polyps, bronchial premalignant lesions, HPV-related cervical dysplasia, dysplastic nevi, carcinoma in situ, etc. While many novel agents are slotted for initial study in the metastatic and/or treatment refractory setting, intralesional immunotherapy may be most effective at bolstering the antineoplastic features of the TME during immunosurveillance eg, via tumor-associated antigens,[6] activating immune effector cells of TDLNs,[13] etc. Techniques including molecular subtyping of premalignant lesions can help to identify patients at highest risk for progression to frank malignancy and also guide intratumoral immunotherapeutic approaches.[53] Furthermore, compared with systemic prevention strategies, it is anticipated that in many cases intralesional immunotherapy can be delivered at lower doses to premalignant lesions, reducing circulating drug levels and systemic immune-related AEs (irAEs) without compromising efficacy. Trial design recommendations for intralesional immunotherapy treatment of premalignant lesions are summarized in box 2.

Some of the expert panel thought that the response of premalignant lesions to preventive intratumoral immunotherapy should be studied, with normalization of histology, regression on imaging, and time-to-event outcomes suggested as response measures in this setting. Some panel members disagreed or were equivocal regarding the study of intratumoral immunotherapy for premalignant lesions, however. There was concern that there is not enough proof-of-concept data to use intratumoral immunotherapy in this setting, particularly as many premalignant lesions never progress to a frank malignancy. For example, although clear local regression has been demonstrated for intratumoral immunotherapy, sustained systemic immunity has yet to be demonstrated. Trials in this population would need to be large and may require long follow-up periods to demonstrate effect, and such costly studies may be premature until efficacy has been more firmly established in more advanced disease. The panel agreed that should trials be undertaken for patients with premalignant lesions, it is particularly important to assess the risk/benefit ratio of intratumoral immunotherapy against the known risk of recurrence and/or progression.

Study population

The panel prioritized the development of intratumoral immunotherapy for premalignant lesions with a higher risk of progression (eg, non-muscle invasive bladder cancer, high-risk cirrhosis, congenital giant nevi), that are not amenable to surgery (eg, familial polyposis syndromes with numerous lesions such as neurofibromatosis), or for which surgery would incur a high level of morbidity (eg, genital, oral cavity/oropharyngeal, and facial lesions). They also prioritized peritumoral and/or regional application of drug (eg, draining LNs) in this setting.

Endpoints for non-randomized trials

Most of the panel agreed that a change in pretreatment versus post-treatment characteristics of the injected premalignant tissue was the best primary endpoint, while a smaller set of respondents prioritized a change in pretreatment versus post-treatment systemic biomarkers or other endpoints. The local effect measured could include reduced dysplasia, immune infiltrate, etc, and serve as proof of efficacy, particularly as there has been a lack of systemic response for intratumoral immunotherapy in this setting. Disease-dependent time to event endpoints identified included time to progression/relapse, development of frank malignancy/invasive disease, or development of new lesions. Regardless of the chosen endpoint, the panel agreed that response should be measured in injected and non-injected lesions whenever possible.

Endpoints for randomized trials

Most of the expert panel agreed that EFS was the best primary endpoint with the remaining panel members prioritizing other endpoints, such as time to progression on first subsequent therapy, disease-specific progression-free survival/death due to disease, progression due to malignancy, local invasion/development of invasive lesions, emergence of histologically similar lesions, or a need for subsequent treatment or imaging. The group agreed that the focus should be on endpoints that are acceptable to regulatory agencies and will lead to approvals, which would most likely be EFS potentially represented by a composite of events in order to expedite study completion. The group agreed that endpoints are necessarily tumor-specific, but overall should have a theme of time to

Box 3 Neoadjuvant intratumoral immunotherapy for clinically non-metastatic disease

- ⇒ Randomized experimental study arms (versus a matched SOC control study arm):
  - ⇒ Adjuvant only SOC: neoadjuvant intratumoral therapy followed by adjuvant SOC systemic therapy.
  - ⇒ Neoadjuvant only SOC: either neoadjuvant intratumoral plus systemic SOC combination therapy with or without continuation of the systemic agent into adjuvant setting versus neoadjuvant intratumoral immunotherapy alone. Randomized studies should be supported by prior mono-arm phase 1/2 results.
  - ⇒ Neoadjuvant followed by adjuvant SOC: neoadjuvant intratumoral plus systemic SOC combination therapy with the SOC systemic agent continued into the adjuvant setting.
- ⇒ Intratumoral placebo control: depends on agent and disease under study; risks of procedure should be weighed against benefits of study blinding and discussed with patients and regulatory agencies as they might consider the intratumoral injection procedure as part of the experimental therapy (therefore not requiring a placebo control to evaluate only the contribution of the injected therapy).
- ⇒ Endpoints for non-randomized trials: centrally assessed pathological response[56–58]; can also consider DFS/EFS/RFS and response as measured by imaging and/or ctDNA pre and post local treatment.
- ⇒ Endpoints for randomized trials: EFS; also consider RFS (ITT population), OS, DFS, disease metastases-free interval, lesion response, pathological response, TRAEs, biological response as measured by immune activity parameters.
- ⇒ Tissue collection timing: when tissue still intact, prior to first injection, status post neoadjuvant therapy and prior to surgery, 3 weeks status post surgery, and at time of progression or recurrence.

avoiding something morbid (eg, surgery, radiation, malignant transformation, loss of heterozygosity, or progression or recurrence of disease on imaging). The group agreed that quality of life may be a relevant endpoint for some diseases, and that sporadic versus genetic lesions will have different endpoints. As the effect of local immune changes on systemic efficacy is still unknown, local immune responses should ideally be developed with a biological correlate.

Sample collection timing

Although the panel agreed that the timing of tissue and/or blood collection depends on the agent and disease under study, they agreed that the ideal time for tissue analysis is prior to the onset of necrosis but after TILs can be demonstrated (a time frame of roughly 48 hours to 1-week postinjection for most agents, and likely within 3–4 weeks of injection for all agents because of the time needed to mount de novo adaptive immunity). Initial tissue sampling should occur when the tumor is still intact (eg, at time of diagnostic biopsy, screening, or enrollment, or prior to the first injection). Blood samples, on the other hand, may be obtained sooner in order to demonstrate an immediate effect. Although serial tissue or blood sampling is ideal, these data may not be logistically feasible (eg, when treatment of the premalignant lesion involves complete resection). When feasible, serial tissue and/or blood samples should be collected at regular intervals for up to 1-year status post (first) injection, taking practical considerations into account (eg, biopsies at the time of procedures such as colonoscopies, injections, etc). The intervals between sample collections will depend on the agent and disease under study.

Neoadjuvant intratumoral immunotherapy for clinically non-metastatic disease

Another high priority clinical setting for intratumoral immunotherapy is in neoadjuvant use. Recent data have suggested that immunotherapy may be more effective when given prior to primary surgical management as compared with adjuvant treatment. Further, this may allow for limited dose exposure and treatment procedures while providing patients with well tolerated but immune potentiating agents. Thus, the panel independently considered the role of intratumoral immunotherapy in the neoadjuvant setting.

For the purposes of this manuscript, the SITC IICT Expert Panel defined clinically non-metastatic disease as any cancer that is resectable or locally treatable with a goal of cure (ie, primarily early-stage disease with associated high rates of cure but potentially including oligometastatic cancer treated with curative intent primary resection and metastasectomy or neoadjuvant chemoradiation). Neoadjuvant intratumoral immunotherapy can lead to high rates of pathological response[54 55] and increases RFS and OS[7] while minimizing systemic toxicity. (Though it is important to note, as discussed in the **Measuring response in phase 2 neoadjuvant and unresectable/metastatic trials** section, data at this time show that pCR is incommensurate of RFS and OS[7 44]). There was a consensus that delivering intratumoral immunotherapy in the neoadjuvant setting with a more competent host immune system (no prior systemic chemotherapy, low immunosuppressive tumor burden, presence of TILs, tumor lymphoid structures (TLS), and intact TDLNs) is the optimal environment to generate tumor-specific systemic immunity against micrometastatic disease that is not yet clinically evident. Given the prospect of cure for patients with locally treated cancers, the safety of an intratumoral immunotherapy agent needs to be established in the unresectable/metastatic setting prior to application to the neoadjuvant/curative setting. Trial design recommendations for intratumoral immunotherapy used to treat clinically non-metastatic disease are summarized in box 3.

Randomized study arms

The panel agreed that the control arm for randomized studies of intratumoral immunotherapy used to treat clinically non-metastatic disease should be SOC treatment, which may entail adjuvant only, neoadjuvant only, or neoadjuvant followed by adjuvant systemic

therapy. The administration of neoadjuvant intratumoral immunotherapy in the experimental arm should occur at least 1–3 weeks prior to local treatment (eg, surgery, radiation) to optimally boost/prime adaptive immunity. Continuation of the intratumoral agent into the adjuvant setting depends on the SOC for the disease under study (see box 3).

Intratumoral placebo control

The panel was divided about whether or not an intratumoral placebo control was required or even preferred in the control arm of a randomized study of intratumoral immunotherapy. Another question raised was the correct vehicle for an injectable drug, for example, saline versus a blank virus. When considering whether or not to use an injectable placebo control, the group agreed that it is also important to consider context (eg, accessibility of lesions, reliability of other biomarkers, etc). Additionally, it is recommended that patient advocacy groups be involved in the discussion of trials and the ethics of including placebo controls from a patient perspective.

Those in favor of using an intratumoral placebo argued that stress and inflammation related to the injection itself may independently alter the TME and confound the effect of the experimental agent. Furthermore, drug approval is often contingent on use of a placebo. Those opposed to using an intratumoral placebo argued that if intratumoral immunotherapy is considered to be a procedure plus drug combination—with the injection being an integral component of the therapy—then the control arm should not include an injectable placebo. Patients may also be unwilling to enroll in studies where they receive an injection without guaranteed drug delivery.

Using a placebo intratumoral vehicle in the control group for a randomized phase 2 study but then forgoing the intratumoral placebo in the larger phase 3 study was one strategy discussed. One instance identified as an acceptable "open label" scenario was the addition of an intratumoral agent to a systemic SOC treatment compared with SOC systemic treatment alone. The group also agreed that it may be more important to have an injectable placebo if the endpoint is more short-term (eg, EFS or degree of tumor regression), however, if the endpoint is more long-term (eg, OS, PFS), then having an injectable placebo may not be as important. Besides the potential negative impact on patient enrollment, if an intratumoral placebo is being considered for incorporation into the control arm of a randomized study, then the potential for harm to the patient with the injection should be carefully weighed against the benefits of study blinding, and these risks should be discussed with patients and regulatory agencies. Alternatively, agencies might consider intratumoral placebo as a sham surgery bringing futile risks and treatment burden to patients, and prefer evaluating the intratumoral injection procedure and the injected therapy as a whole.

Endpoints for non-randomized trials

The panel was divided over the most important primary endpoint for non-randomized studies of neoadjuvant intratumoral immunotherapy. Many members agreed that pathological response of the injected lesion(s) is a reliable primary endpoint. Some members strongly argued that EFS should be included (and correlated to pCR and partial pathological response (pPR) rates in injected and non-injected lesions) as a primary endpoint in non-randomized studies given that there is no established association between pathological response and survival endpoints for intratumoral therapy, and therefore, pathological response is not an accurate endpoint. Overall, the group still favored this endpoint particularly in instances where a good ORR had been demonstrated in earlier phase trials. As pathological response can be nuanced, the group agreed that it should ideally be evaluated centrally with established criteria,[56–59] presuming that tissue transfer for central evaluation would not cause a prohibitive delay in tissue assessment. The remainder of the group prioritized clinical response on imaging (potentially including positron emission tomography(PET) scan results),[60 61] ctDNA,[62] EFS, and disease-free survival (DFS) or time to relapse. RFS for the intention-to-treat (ITT) population was another proposed endpoint, although this endpoint may be difficult to interpret in the absence of a control arm. R0 resection was another proposed endpoint, although it can be heavily dependent on the surgeon and pathologist.

Endpoints for randomized trials

Many expert panel members agreed that EFS was the most important primary endpoint for randomized trials of neoadjuvant intratumoral immunotherapy, while many others prioritized OS,[63] DFS, RFS (for the ITT population), distant metastasis-free interval (DMFI), response in the injected lesion(s), response in the non-injected lesion(s), response measured in all lesions, or progression of residual tissue, pCR (with a survival secondary endpoint), ctDNA (as a tertiary endpoint), or treatment/procedure-related AEs (TRAEs). The group agreed that survival endpoints such as RFS and EFS are more likely to lead to regulatory approvals.

Sample collection timing

Although the panel agreed that the timing of tissue and/or blood collection depends on the agent under study, they agreed that the ideal time for first tissue collection is when the tumor is still intact (eg, at time of diagnostic biopsy, screening, or enrollment), 2 weeks prior to the first injection, at the time of the first injection, status post neoadjuvant therapy (including prior to and 3 weeks postsurgery), and at the time of progression or recurrence. Blood samples should be obtained just prior to biopsies. Because antitumor efficacy of immunotherapies is time dependent, the timing of surgical resection of the injected lesion is also critical. Because it takes about 3 weeks to mount de novo immunity, significant time might

be needed between the intratumoral immunotherapy, the local response, and the systemic antitumor effect. Therefore, adaptive trial designs and associated tissue sampling timing could be envisioned where the local response is monitored and the time of surgery is adapted to the kinetics of tumor responses (eg, delay surgery until kinetics, as measured by ctDNA or imaged tumor diameter, is declining).

Intratumoral immunotherapy for unresectable/metastatic disease

The panel also considered whether there is a role for intratumoral immunotherapy in patients with unresectable or metastatic cancer. They recognized that this is a challenging population for several reasons, including the often higher volume of tumor burden present, the use of multiple prior lines of treatment and potential prior treatment-related toxicity, and the fact that many of these patients will have immune-resistant tumors. Nonetheless, the panel discussed the role for intratumoral immunotherapy studies in this population.

For the purposes of this manuscript, "unresectable/metastatic disease" is defined as any cancer not amenable to surgical resection that may or may not be amenable to cure with systemic treatment (eg, cutaneous melanoma metastatic to multiple lung lobes). Intratumoral immunotherapy elicits a systemic disease response in injected and non-injected lesions[18] in patients with advanced cancer and can lead to systemic cancer remission,[16 17 64] durable response,[1] and improved OS.[1] Trial design recommendations for intratumoral immunotherapy used in the unresectable/metastatic disease setting are summarized in box 4.

Box 4 Intratumoral immunotherapy for unresectable/metastatic disease

- ⇒ Line of therapy to prioritize for development: in the front-line setting for treatment-naïve disease, when feasible.
  - ⇒ Note: Most experts agreed that front-line is optimal, but some agents may be better suited for subsequent lines of therapy or when resistance occurs.
- ⇒ Randomized experimental study arms:
  - ⇒ Control arm: SOC or physician's choice of therapy when no SOC exists.
  - ⇒ Experimental arm: intratumoral agent+SOC (treatment-naïve); intratumoral agent±SOC, depending on phase 2 data (prior non-immunotherapy treatment); intratumoral agent±failed systemic immunotherapy (prior immunotherapy).
- ⇒ Intratumoral placebo control: should be considered for trials of agents in the front-line setting, when feasible.
- ⇒ Endpoints for non-randomized trials: ORR as measured by RECIST v1.1 (total, injected and uninjected), DOR, depth of response for injected and non-injected lesions. The ratio of injected and non-injected target lesions should be documented and reported.
- ⇒ Endpoints for randomized trials: time-to-event endpoints (eg, OS, PFS, EFS).
- ⇒ Tissue collection timing: at screening and then with postinjection times ideally coordinated with functional imaging (ie, at time of peak CD8 expansion) versus at clinical time points of best response and progression; biopsy of non-injected as well as injected lesions should be pursued.

Line of therapy to prioritize for development

The expert panel was divided about which line of therapy to prioritize for development of intratumoral immunotherapy drugs. Those who prioritized development following progression on prior immunotherapy received to treat metastatic disease argued that the development of novel agents typically starts in later lines of treatment to establish safety and efficacy, with findings from these studies then applied to earlier lines of treatment. In some cases, intratumoral immunotherapy may be used to "prime" tumors that are insensitive to ICB.[16] Acquired resistance to anti-PD-1 has been associated with disrupted type I IFN signaling secondary to acquired mutations in JAK1, JAK2, beta-2-microglobulin,[65] and HLA class I loss particularly in intermediate TMB tumors.[66] These changes, however, may result in tumors that are more sensitive to intratumoral immunotherapy agents. For example, oncolytic viruses may replicate more efficiently in tumor cells lacking intact IFN or JAK-STAT signaling.[67]

In addition to tumor cell status, line of treatment may also influence therapeutic outcomes. Indeed, some panelists argued that intratumoral immunotherapy is always more effective earlier in the disease course (ie, when the host immune system is most intact)[23 66 68–70] and could be used to augment front-line SOC systemic therapy. Some panel members prioritized development following progression on prior immunotherapy received in the adjuvant setting, although this was agreed to be an area where further research is needed. The panel also agreed that some cancers, such as hormone receptor-positive breast cancer, are relatively insensitive to immunotherapy in any line of treatment, and this should also be considered. Conversely, advanced cancers that have acquired genomic instability have typically lost their type I IFN sensitivity.[23 68–70] Therefore, some intratumoral immunotherapies which are type I IFN inducers (eg, TLR or STING agonists, oncolytic viruses) might not be adapted to such subsets of diseases.

Randomized study arms

The expert panel discussed their preferred study arms for randomized trials of intratumoral immunotherapy for unresectable/metastatic cancer in different lines of treatment. The group agreed that the control arm should receive SOC therapy regardless of treatment line. In the event that a SOC option does not exist, for example, for some patients whose cancer has progressed on ≥1 prior line of immunotherapy, physician's choice of treatment is a viable alternative. In the case of patient enrollment according to a tumor agnostic biomarker, then the clinical trial design and size should be discussed with authorities first if the trial intent is registrational.

Most of the panel agreed that addition of intratumoral immunotherapy to SOC treatment should serve

Box 5 Perceived barriers to intratumoral immunotherapy development

- ⇒ Lack of efficacious agents.
- ⇒ Incorrect and/or inconsistent injection technique.
- ⇒ Suboptimal patient selection.
- ⇒ Poor translation from animal to human studies.
- ⇒ Lack of champions for these agents/bias of oncologists favoring systemic agents.
- ⇒ Suboptimal referrals.
- ⇒ Biosafety concerns.
- ⇒ Laborious administration with subpar compensation.
- ⇒ Negative inertia/limited financing and decreased interest from pharmaceutical companies.
- ⇒ Non-validated surrogate endpoints.
- ⇒ Trial and drug administration feasibility concerns.
- ⇒ Cost and complexity of drugs (eg, recombinant viruses and necessity of a cold supply chain at minus 80°C).
- ⇒ Difficulty in coordinating across specialties in the hospital.

as the experimental arm for studies of patients who are immunotherapy-naïve. With the caveat that trial design may be dependent on phase 2 observations, the group agreed that intratumoral immunotherapy with or without SOC treatment should be the experimental arm for patients whose cancer has progressed on ≥ 1 prior line(s) of non-immunotherapy treatment. With the caveat that trial design is often context-dependent, many agreed that the intratumoral agent with or without the failed systemic immunotherapy should serve as the experimental arm for patients whose disease has progressed on a prior line(s) of immunotherapy.

Intratumoral placebo control

The panel agreed that an intratumoral placebo agent is more important for trials of unresectable or metastatic disease in the front-line setting, and regulatory agencies may require a placebo injection in the control arm regardless of treatment-line setting. A broader discussion about the necessity of intratumoral placebos with the FDA may be warranted, particularly for lesions that are not (safely) accessible (eg, esophageal lesions). Caveats of placebo control arms include the potential negative influence on patient enrollment and are still relevant in the metastatic setting, although less impactful. Also, in the context of a very active intratumoral therapy (eg, ORR≥50% in injected lesions), it might not be ethically acceptable to inject a placebo. Patient advocacy groups should also be involved in the discussion of trials and the ethics of including placebo controls.

Endpoints for non-randomized trials

The panel discussed that in order to obtain (accelerated) FDA approval for an agent based on a single-arm, non-randomized study of unresectable or metastatic cancer, the efficacy of that agent must be assessed by a surrogate endpoint deemed reasonably likely to predict clinical benefit[71] and a confirmatory randomized trial must be well underway at the time of accelerated approval[71] (with the potential exception of true orphan diseases). However, it was recognized that conducting a randomized clinical trial in the same setting as the initial single arm trial, for example, where patients have already progressed on SOC, may be challenging, as there may be no SOC with which to compare. Furthermore, in later lines of therapy, the FDA may look for an OS endpoint, which can be challenging to obtain. And while imaging such as with Stein Fojo modeling[72] that isolates and quantifies the behavior of the treatment-resistant fraction of the tumor can give much more "power per patient" in smaller, phase 2 studies, this approach does not scale up well.

Most panel members agreed that clinical response on imaging or, to a lesser degree, pathological response of injected lesion(s) and non-injected lesions, were the most important primary endpoints for non-randomized trials of intratumoral immunotherapy for unresectable/metastatic disease. The group pointed out that while it is necessary to establish local efficacy in this setting (particularly, eg, if the injected lesion is causing significant morbidity), it may not be sufficient. Response in non-injected lesions, as well as of overall disease, is particularly important to measure for metastatic disease, and duration and depth of response should be measured in addition to ORR, which can be misleading when reported in isolation. OS and PFS (as measured by an immune response criteria allowing for progression before response) were also discussed, although the group acknowledged that itRECIST and iRECIST are exploratory and regulatory agencies still require proof of efficacy via RECIST v1.1 (with the modification that progression before response should be allowed). A surrogate endpoint in phase 2 trials to determine efficacy in a different population than the phase 1 (safety/pharmacodynamics) population (eg, phase 1 population consists of pretreated patients, phase 2 population consists of treatment-naïve patients) was discussed, but ultimately if no efficacy is demonstrated in phase 1, it is difficult to support continuation of a drug into a phase 2 trial.

Endpoints for randomized trials

The panel agreed that OS, EFS (eg, PFS, disease metastases-free survival (DMFS), or potentially as a composite of progression, initiation of next line therapy, and death), and/or response in all lesions were the best primary endpoints for randomized trials of intratumoral immunotherapy in the unresectable/metastatic disease setting. The group discussed that a time-to-event endpoint is needed for approval, and that response in injected versus non-injected lesions should be measured separately with annotation for location (eg, liver). Response should be measurable by RECIST v1.1 and DOR should be measured as well. If PFS is to be used as an endpoint, then progression outside of the treatment field is especially important to

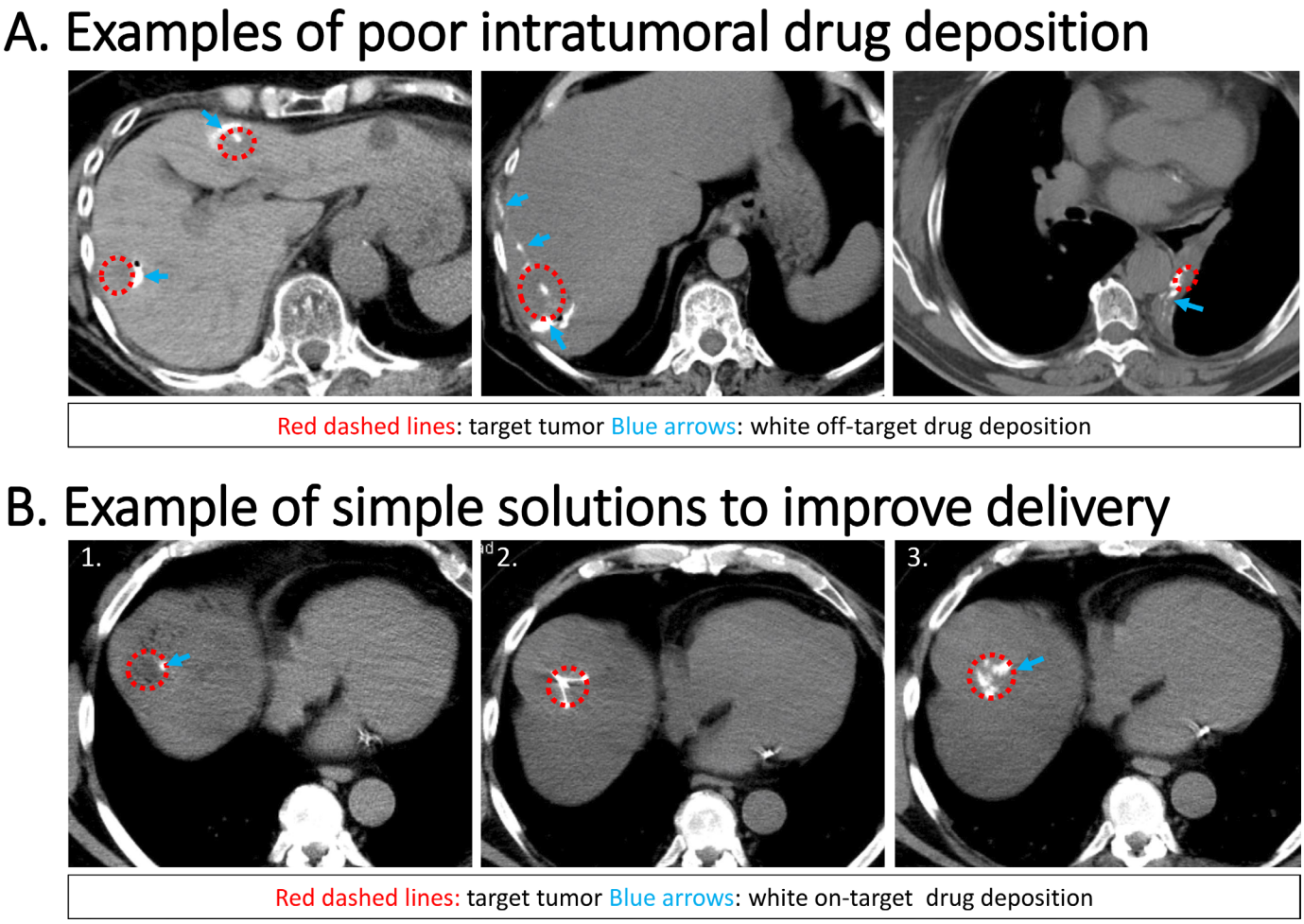

Figure 1 Intratumoral drug deposition. (A) Examples of poor intratumoral drug deposition. (B) Example of simple solutions to improve delivery. Percutaneous delivery using a conventional end-hole needle led to minimal drug deposition within the tumor (B1). Repeat injection was performed using a multipronged needle (B2). Injection via multipronged needle led to substantial improvement in intratumoral drug delivery (B3).

measure. Of note, progression per RECIST v1.1 can be misleading with immunotherapy agents. Indeed, initial inflammation reactions to the intratumoral therapy can increase draining LNs above the 15 mm size limit or convert distant microscopic lesions to measurable, and therefore, count as a new lesions and classify the patient as a progressor although those can be due to transient inflammation reactions. Thus, initial progression before response should be allowed and confirmation of progression required when assessing both ORR and PFS.

Sample collection timing

The panel agreed that while the timing of tissue collection depends on the agent being studied, ideal times to collect samples included at screening (for tissue, to avoid confounding TRAEs and to avoid interfering with the first injection) and at the time of or just prior to each injection (for blood). The group discussed functional (eg, CD8-based or granzyme-based) imaging, for example, to coordinate sample collection with peak CD8 expansion[73]; even in just a subset of patients these data would be informative as the optimal time for biopsy varies widely based on disease and therapy. Clinical markers (eg, at time of best response and time of progression) could also be used to guide tissue acquisition. Several post-treatment time points for tissue collection were discussed, including monthly intervals up to 1 year, 1–3 weeks status post first injection (with a risk of necrosis and/or patient refusal beyond this point), and later time points if feasible to capture durable inflammatory immune responses. Importantly, the group agreed that non-injected lesions should be biopsied as well, particularly when correlated with functional imaging, as this tissue can provide great insight into the response and mechanism of action of the drug. Patients would need a particularly thorough explanation about biopsy of non-injected lesions as part of a shared informed consent and decision-making process.

BARRIERS TO INTRATUMORAL IMMUNOTHERAPY DEVELOPMENT

The panel identified multiple barriers to the development of intratumoral immunotherapy that are summarized in box 5.

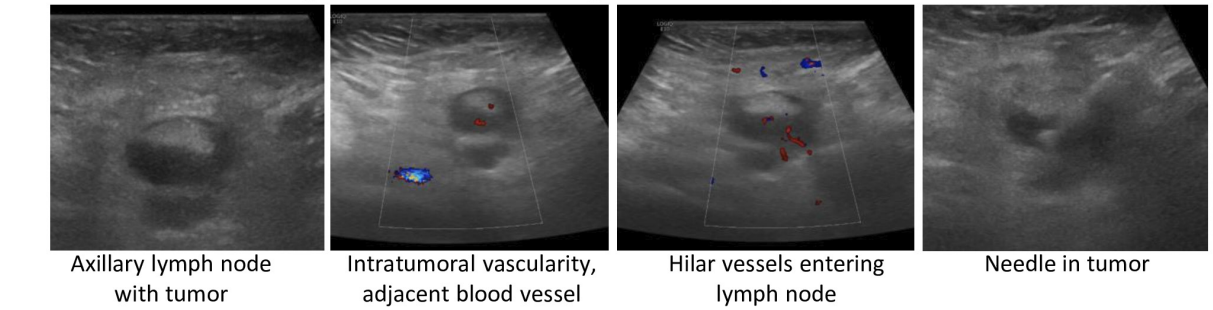

Figure 2 Variables affecting injection technique. (A) Ultrasound images demonstrating vascularity of a tumor-containing LN. (B) Liver metastasis with gray scale (B1) and contrast-enhanced (B2) ultrasound revealing hypervascularity relative to liver parenchyma. (C) Liver metastases with extensive internal necrosis. (D) LN with gray scale and contrast-enhanced ultrasound. Gray scale (D1) and contrast-enhanced (D2) ultrasounds of a subcutaneous LN demonstrating an arterially enhanced, without parenchymal washout, LN (white arrows) and a non-enhanced, likely necrotic LN (yellow arrows). LN, lymph node.

The panel cited inconsistent and/or incorrect injection technique as a major obstacle in the development of intratumoral immunotherapy. Injection technique, drug formulation and tumor stiffness all influence drug delivery, and off target injection can lead to decreased efficacy and increased TRAEs[74] (see figure 1). Variables in injection technique identified by the group included degree of extravasation, injection into a necrotic area of a tumor (see figure 2) or a wrong-sized tumor, variable pressure with agent delivery, number of tumor punctures, and level of operator expertise/experience. Please refer to the **Guidance on Administration of Localized Immunotherapy in Solid Tumors and Lymphomas** supplement for this manuscript for a detailed discussion and illustrations of injection technique. The group concurred that a standardized process for monitoring and documenting drug injection/application (eg, needle position, proximity of vessels, percentage of agent injected versus extravasated, identification/targeting of tumor (versus necrotic) tissue, etc) is critical for the development of intratumoral immunotherapy.

Suboptimal patient selection was cited as another major concern in the design of intratumoral immunotherapy trials. The panel agreed that patients should be distinguished by tumor biology, not just stage, histology, and line of treatment. Furthermore, studies need to enroll a patient population that will lend itself to demonstrating an effect of the drug, for example, patients need to have lesions measurable by RECIST and that are most likely to benefit from intratumoral immunotherapy.

HIGH-IMPACT AREAS TO PRIORITIZE IN INTRATUMORAL IMMUNOTHERAPY DEVELOPMENT

The expert panel identified the following settings for which intratumoral immunotherapy may have the greatest potential to make a high impact: (1) the neoadjuvant setting, which allows for a minimal or set number of procedures and will produce a resection specimen for tissue analysis, (2) injection of either primary or metastatic liver lesions (or other immunologically "cold" lesions) in order to change the local TME and potentially help systemic agents work better, (3) single-agent intratumoral immunotherapy for patients with contraindications to systemic ICB (eg, solid organ transplant recipients) or who do not respond to ICB (eg, patients with B-cell malignancies), (4) early-stage or adjuvant in situ vaccination to establish ablative immunosurveillance for cancers likely to recur (eg, HCC), and (5) further development of pharmaceutical technologies to improve intratumoral drug formulations/delivery (eg, new medical devices/formulations such as hydrogels, robotic endoscopic injection). When used in the unresectable/metastatic setting, the group favored development of intratumoral immunotherapy for locoregionally advanced, unresectable disease, and careful consideration of intratumoral-specific endpoints. The group also prioritized concomitant treatment (eg, with radiation and/or chemotherapy) as intratumoral immunotherapy can favorably alter the TME.[75] These high impact niches are listed in box 6.

Box 6 High-impact areas to prioritize in intratumoral immunotherapy development.

- ⇒ Neoadjuvant setting.
- ⇒ Immunologically cold lesions.
- ⇒ Patients who have progressed on prior ICB.
- ⇒ As monotherapy for patients with contraindications or non-response to systemic ICB.
- ⇒ In situ immunization of early-stage tumors to establish immunosurveillance and avoid relapse or decrease disease kinetics.
- ⇒ Development of technology to improve intratumoral drug delivery.
- ⇒ Locoregionally advanced, unresectable disease.
- ⇒ Concomitant treatment with radiation and/or chemotherapy

CONCLUSION

Intratumoral immunotherapy is a potentially effective monotherapy when used in the optimal disease settings, but also may increase the effectiveness of systemic treatments without the cost of added toxicity. Intratumoral immunotherapy may expand the benefit of immunotherapy to patients with ICB-refractory or immunologically cold tumors and may expand access of immunotherapy to patients with contraindications to systemic treatment. Several paradigm shifts in intratumoral immunotherapy development must occur before the potential of these drugs can be realized, however. Tumor biology must be accounted for when designing clinical trials. Early-phase trials of widely metastatic and/or pretreated disease are likely not a suitable platform to demonstrate intratumoral immunotherapy activity. Study endpoints must reflect the mechanism of action of each agent as well as each unique disease setting. And finally, the intratumoral administration of immunotherapy must be standardized in a way that will minimize off-target drug delivery and maximize efficacy and consistency of the agent. Intratumoral immunotherapy must address a number of specific medical needs and it is expected that it will eventually deliver on that endeavor. The recent negative results of some of the initial registration attempts (ie, beyond T-VEC as monotherapy in melanoma) should not deter health agencies from supporting future development of intratumoral immunotherapy by pharmaceutical and academic investigators in the right clinical setting.

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